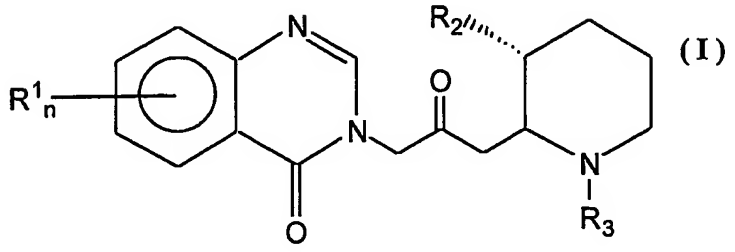
CLAIMS

1. A polymeric delivery system for sustained release administration of a quinazolinone derivative of formula (I)



(I)

wherein: n=1-2

R_1 which may be the same or different at each occurrence is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, phenyl and lower alkoxy;

R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and pharmaceutically acceptable salts thereof,

wherein the quinazolinone is released at a therapeutically effective dose for a period of at least one month.

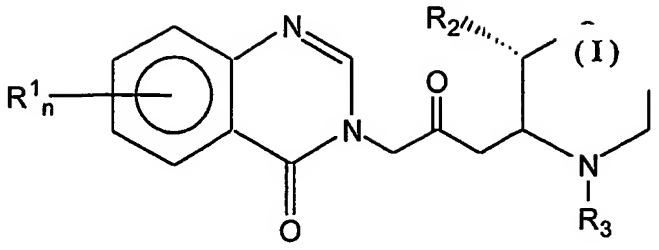
2. The polymeric delivery system of claim 1 wherein the delivery system is formulated for local administration or topical administration to a target site in a subject.

3. The delivery system of claim 2, wherein the route of administration is selected from implantation, subcutaneous injection or deposition within a body cavity.

4. The delivery system of claim 1, wherein the quinazolinone derivative of formula (I) is halofuginone.

5. The delivery system of claim 3, wherein the delivery system is formulated as an implant other than as a coating for a stent.

6. A polymeric delivery system for sustained release of a quinazolinone derivative of formula (I):



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R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and pharmaceutically acceptable salts thereof;

the polymeric delivery system comprising biocompatible two-phase polymeric beads comprising a core compartment comprising a water-in-oil emulsion surrounded by a polymeric shell compartment comprising a biocompatible polymer, wherein the discontinuous aqueous phase of the core compartment of the polymeric beads comprises the quinazolinone derivative of formula (I).

7. The delivery system of claim 6, wherein the biocompatible polymer is a natural or synthetic hydrophilic polymer.

8. The delivery system of claim 7, wherein the biocompatible hydrophilic polymer is a polysaccharide or a protein.

9. The delivery system of claim 8, wherein the polysaccharide is selected from: alginate, dextran, cellulose, cellulose derivatives, dextran sulfate, chondroitin sulfate, heparan sulfate, heparin, keratan sulfate, dermatan sulfate, and algal polyglycan sulfates.

10. The delivery system of claim 9, wherein the polysaccharide polymer is alginate.

11. The delivery system of claim 8, wherein the protein is selected from: gelatin, collagen, elastin, fibrin and albumin.

12. The delivery system of claim 11, wherein the protein is gelatin.

13. The delivery system of claim 6, wherein the quinazolinone derivative of formula (I) is halofuginone.

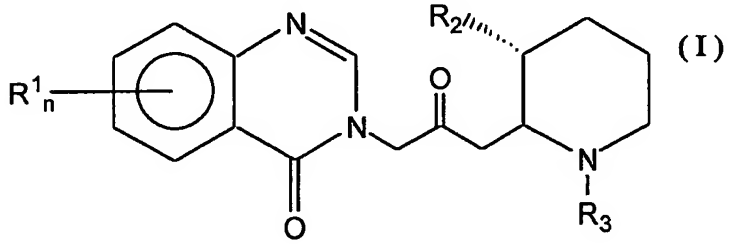
14. The delivery system of claim 6, wherein the quinazolinone derivative of formula (I) is released at a therapeutically effective concentration for a time period ranging from a several days to a several months.

15. The delivery system of claim 6, wherein the delivery system is formulated for local administration or topical administration to a target site.

16. The delivery system of claim 15, wherein the route of administration is selected from implantation, subcutaneous injection or deposition within a body cavity

17. The delivery system of claim 6, wherein the polymeric beads are dispersed within an oil-based formulation or water-based selected from an oily suspension, emulsion, cream and gel.

18. A polymeric delivery system for local sustained release of a quinazolinone derivative of formula (I):



(I)

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R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and pharmaceutically acceptable salts thereof;

the polymeric delivery system comprising a biocompatible polymeric film wherein the quinazolinone derivative of formula (I) is homogeneously dispersed within the film.

19. The delivery system of claim 18, wherein the biocompatible polymer is a selected from a synthetic biodegradable and a synthetic non-biodegradable polymer.

20. The delivery system of claim 19, wherein the synthetic polymer is selected from: polyacrylic acid polymers, polylactic acid polymers, polycaprolactone polymers, polyglycolic acid and various copolymers thereof.

21. The delivery system of claim 20, wherein the synthetic biocompatible polymer is polycaprolactone.

22. The delivery system of claim 18, wherein the polymeric film is a coating of an article.

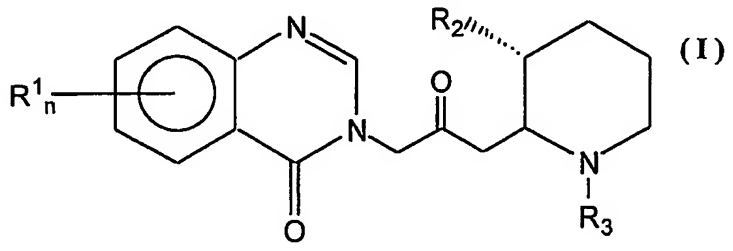
23. The delivery system of claim 18, wherein the quinazolinone derivative of formula (I) is halofuginone.

24. The delivery system of claim 18, wherein the quinazolinone derivative of formula (I) is released at a therapeutically effective concentration for a time period ranging from a several days to a several months.

25. The delivery system of claim 18, wherein the delivery system is suitable for a route of administration selected from subcutaneous implantation and deposition within a body cavity.

26. The delivery system of claim 18, wherein the delivery system is suitable for application topically at a target site of a subject.

27. A polymeric delivery system for sustained release of a quinazolinone derivative of formula (I)



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R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and pharmaceutically acceptable salts thereof;

the delivery system comprising a polymeric complex comprising at least one type of biocompatible negatively-charged polymeric molecule conjugated through electrostatic interactions to the quinazolinone derivative of formula (I), said quinazolinone derivative of formula (I) having a positive charge at physiological pH.

28. The delivery system of claim 27, wherein the negatively charged biocompatible polymer is a synthetic or natural biocompatible polymer.

29. The delivery system of claim 28, wherein the synthetic or natural polymer is selected from polyacrylic acid polymers, alginate polymers, polylactic acid polymers, polyglycolic acid and various copolymers thereof.

30. The delivery system of claim 29, wherein the negatively charged biocompatible polymer is alginate or polyacrylic acid.

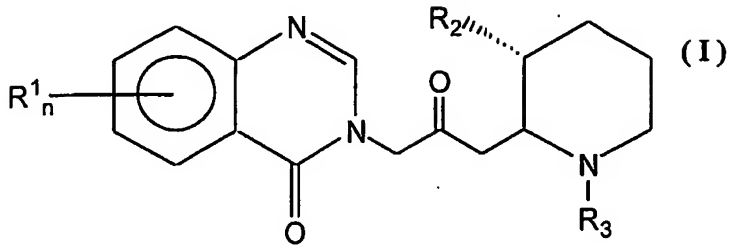
31. The delivery system of claim 27, wherein the quinazolinone derivative of formula (I) is halofuginone.

32. The delivery system of claim 27, wherein the quinazolinone derivative of formula (I) is released at a therapeutically effective concentration for a time period ranging from a several days to a several months.

33. The delivery system of claim 27, wherein the delivery system is suitable for a route of administration selected from subcutaneous implantation and deposition within a body cavity.

34. The delivery system of claim 27, wherein the delivery system is suitable for application topically at a target site of a subject.

35. A polymeric delivery system for sustained release of a quinazolinone derivative of formula (I):



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R_2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy;

R_3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; and pharmaceutically acceptable salts thereof,

the polymeric delivery system comprises biocompatible polymeric beads in suspension, wherein the polymeric beads comprise the quinazolinone derivative of formula (I).

36. The delivery system of claim 35, wherein the biocompatible polymer is a natural or synthetic hydrophilic polymer.

37. The delivery system of claim 36, wherein the biocompatible natural polymer is selected from a polysaccharide and a protein.

38. The delivery system of claim 37, wherein the polysaccharide is selected from: alginate, dextran, cellulose, cellulose derivatives, dextran sulfate, chondroitin sulfate, heparan sulfate, heparin, keratan sulfate, dermatan sulfate, and algal polyglycan sulfates.

39. The delivery system of claim 38, wherein the polysaccharide polymer is alginate.

40. The delivery system of claim 37, wherein the protein is selected from: gelatin, collagen, elastin, fibrin and albumin.

41. The delivery system of claim 40, wherein the protein is gelatin.

42. The delivery system of claim 35, wherein the quinazolinone derivative of formula (I) is halofuginone.

43. The delivery system of claim 35, wherein the quinazolinone derivative of formula (I) is released at a therapeutically effective concentration for a time period ranging from a several days to a several months.

44. The delivery system of claim 35, wherein the delivery system is suitable for a route of administration selected from implantation, subcutaneous injection and deposition within a body cavity.

45. The delivery system of claim 35, wherein the delivery system is formulated for topical administration to a target site in a subject.

46. The delivery system of claim 35, wherein the polymeric beads are dispersed within an oil-based or water-based formulation selected from an oily suspension, emulsion, cream or gel.

47. A method of preparing the biocompatible polymeric beads of claim 6 comprising:

a. mixing an aqueous suspension of the quinazolinone derivative of formula (I) in an oily phase to form a water-in-oil emulsion;
b. homogenizing the mixture of step (a);
c. applying a polymeric shell around small droplets of the emulsion by means of core/shell extrusion, and
d. solidifying the shell to form two phase core-and-shell-structured polymeric beads.

48. A method of preparing the polymeric film of claim 18 comprising:

a. dissolving the quinazolinone derivative of formula (I) in an organic solvent to form a drug solution;
b. mixing the polymer in suitable solvent to form a polymeric solution;
c. mixing the drug solution with the polymeric solution; and
d. evaporating the polymer solvent to form the polymeric films comprising said quinazolinone derivative of formula (I) homogenously dispersed therein.

49. A method of preparing the biocompatible delivery system of claim 27 comprising:

a. dissolving the quinazolinone derivative of formula (I) in an aqueous phase to form a drug solution;

b. mixing the polymer in suitable aqueous phase to form a polymeric solution;

c. mixing the drug solution with the polymeric solution for sufficient time to form polymeric complexes; and

d. precipitating the polymeric complexes.

50. A method of preparing the biocompatible delivery system of claim 35 comprising:

a. suspending the quinazolinone derivative of formula (I) in an aqueous solution to form a drug suspension;

b. mixing the polymer in suitable solvent to form a polymeric solution;

c. mixing the polymeric solution with a cross linking agent and the drug suspension to form polymeric beads comprising said quinazolinone derivative of formula (I).

51. A method of delivering a stable therapeutic concentration of the quinazolinone derivative of formula (I), comprising: administering to a subject in need thereof the biocompatible polymeric delivery system according to claim 6, wherein said delivery system continuously delivers a stable therapeutic concentration of said quinazolinone derivative of formula (I) for a period of time ranging from days to months.

52. The method of claim 51 wherein the quinazolinone derivative of formula (I) is halofuginone.

53. A method of treating or inhibiting a disease selected from a neoplastic disease, restenosis, a disease associated with angiogenesis and a disease associated with fibrosis, comprising administering to a subject in need thereof a quinazolinone derivative of formula (I) in a biocompatible polymeric delivery system according to claim 6, the delivery system continuously delivering a stable therapeutic concentration of the

quinazolinone derivative for a period of time ranging from days to months, thereby treating the disease.

54. The method of claim 53 wherein the quinazolinone derivative of formula (I) is halofuginone.

55. A method of delivering a stable and local therapeutic concentration of a quinazolinone derivative of formula (I), comprising: administering to a subject in need thereof the biocompatible polymeric delivery system according to claim 18, wherein the delivery system continuously delivers a stable therapeutic concentration of the quinazolinone derivative of formula (I) for a period of time ranging from days to months.

56. The method of claim 55 wherein the quinazolinone derivative of formula (I) is halofuginone.

57. A method of treating or inhibiting a disease selected from a neoplastic disease, restenosis, a disease associated with angiogenesis and a disease associated with fibrosis comprising administering to a subject in need thereof a quinazolinone derivative of formula (I) in a biocompatible polymeric delivery system according to claim 18, the delivery system continuously delivering a stable therapeutic concentration of the quinazolinone derivative for a period of time ranging from days to months, thereby treating the disease.

58. The method of claim 57 wherein the quinazolinone derivative of formula (I) is halofuginone.

59. A method of delivering a stable and local therapeutic concentration of the quinazolinone derivative of formula (I) comprising: administering to a subject in need thereof the biocompatible polymeric delivery system according to claim 27, wherein the delivery system continuously delivers a stable therapeutic concentration of said quinazolinone derivative of formula (I) for a period of time ranging from days to months.

60. The method of claim 59 wherein the quinazolinone derivative of formula (I) is halofuginone.

61. A method of treating or inhibiting a disease selected from a neoplastic disease, restenosis, a disease associated with angiogenesis and a disease associated with fibrosis comprising administering to a subject in need thereof a quinazolinone derivative of formula (I) in a biocompatible polymeric delivery system according to claim 27, wherein the delivery system continuously delivers a stable therapeutic concentration of the quinazolinone derivative for a period of time ranging from days to months, thereby treating the disease.

62. The method of claim 61 wherein the quinazolinone derivative of formula (I) is halofuginone.

63. A method of delivering a stable and local therapeutic concentration of the quinazolinone derivative of formula (I) comprising: administering to a subject in need thereof the biocompatible polymeric delivery system according to claim 35, wherein the delivery system continuously delivers a stable therapeutic concentration of the quinazolinone derivative of formula (I) for a period of time ranging from days to months.

64. The method of claim 63 wherein the quinazolinone derivative of formula (I) is halofuginone.

65. A method of treating or inhibiting a disease selected from a neoplastic disease, restenosis, a disease associated with angiogenesis and a disease associated with fibrosis comprising administering to a subject in need thereof a quinazolinone derivative of formula (I) in the biocompatible polymeric delivery system of claim 35, wherein said delivery system continuously delivers a stable therapeutic concentration of halofuginone for a period of time ranging from days to months, thereby treating the disease.

66. The method of claim 65 wherein the quinazolinone derivative of formula (I) is halofuginone.

67. An implant comprising the polymeric delivery system of claim 6.

68. An implant comprising the polymeric delivery system of claim 18.

69. An implant comprising the polymeric delivery system of claim 27.

70. An implant comprising the polymeric delivery system of claim 35.